UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Oral Argument Requested

MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' JOINT MOTION TO EXCLUDE THE OPINIONS OF STEPHEN HECHT, PH.D.

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Cases

Rules

Defendants' Executive Committee, on behalf of all Defendants in this litigation, respectfully submits this Memorandum of Law in Support of Defendants' Joint Motion to Exclude the Opinions of Stephen S. Hecht, Ph.D., pursuant to Federal Rules of Evidence 104, 403, and 702 ("Motion").

INTRODUCTION

Dr. Hecht's "general causation" opinion is limited to a single, boilerplate sentence regurgitated over and over again with regard to each Manufacturer Defendant: that low levels of NDMA and NDEA "caused an unreasonably dangerous and unacceptable risk of causing or substantially contributing to the causation of cancer for those ingesting" the valsartan containing drugs ("VCDs"). (*See, e.g.*, Ex. A, Hecht Rep. 22-23). The remainder of his report is limited to root cause and liability, neither of which is at issue at this stage of the litigation. As Dr. Hecht's bare-bones general causation opinions are not based on any reliable methodology and will not assist the trier of fact, Plaintiffs do not meet their burden of demonstrating that his opinion and testimony meet the requirements for admissibility under Rule 702 of the Federal Rules of Evidence ("Rule 702"). Accordingly, Defendants' Motion to strike Dr. Hecht's opinions should be granted.

FACTUAL AND PROCEDURAL BACKGROUND

This litigation arises from recalls of certain drug products containing the active pharmaceutical ingredient ("API") valsartan announced by the U.S. Food and

Drug Administration ("FDA") beginning in July 2018 due to the unexpected presence of an impurity, N-nitrosodimethylamine ("NDMA").[1] The VCDs at issue are generic versions of certain branded angiotensin II receptor blocker ("ARB") drugs approved primarily for the treatment of hypertension and heart failure. In July 2018, Defendants, with guidance from the FDA, began announcing voluntary recalls of certain VCDs after trace amounts of NDMA were detected in some, but not all, lots of valsartan. These recalls later expanded to include a second unexpected impurity in valsartan, N-nitrosodiethylamine ("NDEA").[2]

No regulatory agency in the world has classified NDMA or NDEA as a human carcinogen because there are insufficient data to make that determination. Instead, regulatory agencies, taking a conservative approach, have generally classified NDMA and NDEA only as "probable" or "likely" human carcinogens based on the limited data from animal studies. The International Agency for Research on Cancer ("IARC"), for example, has classified NDMA and NDEA as Group 2A

[1] Ex. B, FDA News Release, "FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity," July 13, 2018, *available at* https://www.fda.gov/news-events/press-announcements/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following-detection-impurity.

[2] *See, e.g.*, Ex. C, FDA News Release, "FDA provides update on its ongoing investigation into valsartan products; and reports on the finding of an additional impurity identified in one firm's already recalled products," Sep. 13, 2018, available at https://www.fda.gov/news-events/press-announcements/fda-provides-update-its-ongoing-investigation-valsartan-products-and-reports-finding-additional.

carcinogens.[3] Group 2A carcinogens have "***limited evidence of carcinogenicity in humans***," meaning "[a] positive association has been observed between exposure to the agent, mixture or exposure circumstance and cancer for which a causal interpretation is considered by the Working Group to be credible, ***but chance, bias or confounding could not be ruled out with reasonable confidence***."[4]

Importantly, however, these classifications are hazard based, not risk based, and do not take into account the dose—a primary consideration in the general causation question at hand. As the FDA has noted, NDMA is common "in water and foods, including cured and grilled meats, dairy products and vegetables."[5] "Everyone is exposed to some level of nitrosamines" and "[n]itrosamine impurities may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time, but a person taking a drug that contains nitrosamines

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[3] *See* Ex. D, IARC, *N-Nitrosodimethylamine*, *available at* https://inchem.org/documents/iarc/vol17/n-nitrosodimethylamine.html (last accessed Oct. 11, 2021) (classifying NDMA as a Group 2A carcinogen); Ex. E, IARC, *N-Nitrosodiethylamine*, *available at* https://inchem.org/documents/iarc/vol17/n-nitrosodiethylamine.html (last accessed Oct. 11, 2021) (classifying NDEA as Group 2A carcinogen).

[4] *See* Ex. F, IARC, *Evaluation*, *available at* https://inchem.org/documents/iarc/monoeval/eval.html (last accessed Oct. 11, 2021) (emphasis added).

[5] *See* Ex. G, FDA, "Information about Nitrosamine Impurities in Medications," *available at* https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications (last accessed Oct. 25, 2021).

at-or-below the acceptable daily intake limits every day *for 70 years* is not expected to have an increased risk of cancer."[6]

Prior to June 2018, the United States Pharmacopeia (USP) monograph testing for VCDs did not include testing for nitrosamines. Subsequent to the recalls, the FDA developed and published novel testing methods designed to detect the trace levels of nitrosamine impurities in the VCDs.[7] While the FDA has now issued guidance setting levels deemed acceptable for production purposes, it has never made any pronouncement that higher levels are inherently "unsafe" or cause cancer.

In bifurcating and prioritizing the general causation question, the Court recognized Plaintiffs' challenge in establishing general causation, noting it pertains to the class action claims as much as the personal injury claims:

> There's a number of people who claim I understand that they've contracted cancer from taking this drug. It's probably going to be a heavy lift to prove that […] I think that causation carries over into the other cases that are pending because, you know, if the contamination is not dangerous, then maybe you don't have such a great argument that you should get your money back for paying for it.

[6] *Id.* (emphasis added).

[7] *See* Ex. H, FDA, "FDA Updates and Press Announcements on Angiotensin II Receptor Blocker (ARB) Recalls (Valsartan, Losartan, and Irbesartan)," *available at* https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan (last accessed Oct. 25, 2021).

(Ex. J, 3-27-19 Hrg. Tr. at 5:9-16). This Court likewise appreciated that cancer cannot be homogenized for purposes of evaluating general causation and that Plaintiffs must meet their general causation burden on each and every cancer alleged:

> There has to be a reckoning at some point as to all these cancer claims, and they can't -- I don't think at the end of the day the science is going to support … the claims of some of these plaintiffs that every conceivable cancer out there is caused by the impurities in the [VCDs]. And there is going to have to be a winnowing of that, and there's going to be a focus by the plaintiffs on what actual cancers they claim have been caused or will be caused in the future by these [VCDs].

(Ex. K, 7-29-20 Hrg. Tr. at 43:21-44:6, 44:16-18).

In response to the Court's order to "disclose the types of cancer for which they will provide expert reports to proceed to the general causation *Daubert* hearing in the MDL" (Dkt. 640), Plaintiffs disclosed the following cancers: bladder, blood, breast, colorectal/intestinal, esophageal, gastric, kidney, liver, lung, pancreatic, pharyngeal, prostate and uterine, (Dkt. 706). To date, Plaintiffs have not sought to amend this disclosure for good cause.

Plaintiffs produced the reports of five general causation experts: David Madigan, Ph.D, Stephen Lagana, M.D., Stephen Hecht, Ph.D, Dipak Panigrahy, M.D., and Mahyar Etminan, PharmD, MSc. Notably, none of Plaintiffs' experts addresses claims of breast or uterine cancer in their expert reports.[8] In response,

[8] For this reason alone, any Plaintiff who claims the VCDs caused them to develop breast or uterine cancer should be dismissed.

Defendants produced the reports of nine general causation experts. In addition to opining on the lack of general causation, Defendants' experts identified significant flaws with the qualifications, scientific methodology, and reliability of Plaintiffs' general causation experts. The deposition testimony of Plaintiffs' experts crystalized these flaws.

LEGAL STANDARDS

I. PLAINTIFFS' BURDEN ON GENERAL CAUSATION.

General causation is whether a substance can cause an increased risk of a particular injury or condition in the general population. *See McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1239 (11th Cir. 2005). In contrast, specific causation is whether a substance caused a particular individual's injury. *Id.* Plaintiffs bear the burden of establishing that their experts' general causation testimony is admissible by a preponderance of the evidence. *See Ctr. City Periodontists, P.C. v. Dentsply Int'l, Inc.*, 321 F.R.D. 193, 202 (E.D. Pa. 2017) (citing *Padillas v. Stork-Gamco, Inc.*, 186 F.3d 412, 418 (3d Cir. 1999)); *Warren Distrib. Co. v. InBev USA L.L.C.*, 2010 WL 2179167, at *3 (D.N.J. May 28, 2010) (Kugler, J.) (citing *Kannankeril v. Terminix Int'l, Inc.*, 128 F.3d 802, 806 (3d Cir. 1997)).

Here, the general causation question is whether NDMA or NDEA can cause the cancers alleged by Plaintiffs at exposure levels people may have plausibly experienced. *In re Roundup Prod. Liab. Litig.*, 390 F. Supp. 3d 1102, 1111 (N.D.

Cal. 2018) (citing *Anderson v. Liberty Lobby, Inc.,* 477 U.S. 242, 249-50 (1986) ("To carry their burden during this phase of the litigation, the plaintiffs must put forward admissible evidence supporting their claim that [a substance] is capable of causing [the alleged disease] at exposure levels humans might have experienced.")); *see also Hardeman v. Monsanto Co.*, 997 F.3d 941, 963 (9th Cir. 2021); *In re Zoloft (Sertralinehydrochloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 483, 487 (E.D. Pa. 2016), *aff'd sub nom. In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787 (3d Cir. 2017); *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d 781, 793 (N.D. Cal. 2020) (quoting *In re Hanford Nuclear Rsrv. Litig.*, 292 F.3d 1124, 1133 (9th Cir. 2002)).

Further, because cancer occurs in the general population irrespective of NDEA or NDMA exposure, Plaintiffs must put forward admissible testimony that ***each*** of the specific types of cancer alleged "could possibly be attributable to [the] particular drug[s]" in this case. *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 533 (W.D. Pa. 2003); *see also Hostetler v. Johnson Controls, Inc.*, 2020 WL 5543081, at *2 (N.D. Ind. Sept. 16, 2020) (holding that "in order for the Plaintiffs to face an increased risk of developing adverse health effects, the exposures they experienced must be capable of causing those effects" and "each individual plaintiff's exposure [must] place[ ] that individual at an increased risk"). The general causation inquiry must also account for background risk and whether a product or

agent increases the risk of the adverse effects compared to the risk the general population faces, and if it does not, the likelihood that the product harmed plaintiffs is reduced. *See McClain*, 401 F.3d at 1239-43.

For the reasons set forth herein and in Defendants' concomitantly filed briefs, Plaintiffs have failed to meet this burden.

A. Admissibility of Expert Testimony Under Rule 702

"[T]rial courts must perform a gatekeeping function to ensure the relevance and reliability of expert testimony." *In re Johnson & Johnson Talcum Powder Prod. Mktg., Sales Practices & Prod. Litig.*, 509 F. Supp. 3d 116, 130 (D.N.J. 2020) (citing *Daubert v. Merrell Dow Pharms., Inc.,* 509 U.S. 579, 589 (1993)); *see also In re Paulsboro Derailment Cases*, 746 Fed. Appx. 94, 98 (3d Cir. 2018) (Vanaskie, J.) (citing *Daubert*, 509 U.S. at 589). The Court's gatekeeping "role is especially sensitive in cases 'where the plaintiff claims that exposure to a toxic substance caused his injury, [because a] jury may blindly accept an expert's opinion that conforms with their underlying fears of toxic substances without carefully understanding or examining the basis for that opinion.'" *Whiting v. Bos. Edison Co.*, 891 F. Supp. 12, 24 (D. Mass. 1995). It is within the Court's "discretion to exclude unreliable portions of an expert's testimony '[w]hen faced with . . . testimony that contains both reliable and unreliable opinions.'" *Johnson & Johnson*, 509 F. Supp.

3d at 139-40 (quoting *In re Pfizer Inc. Securities Litig.*, 819 F.3d 642, 665 (2d Cir. 2016)).

Rule 702 governs the Court's gatekeeping function and the admission of expert testimony. *See* FED. R. EVID. 702. Rule 702 provides that a witness "qualified as an expert by knowledge, skill, experience, training or education" may testify if:

> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
> (b) the testimony is based on sufficient facts or data;
> (c) the testimony is the product of reliable principles and methods; and
> (d) the expert has reliably applied the principles and methods to the facts of the case.

FED. R. EVID. 702. In short, Rule 702 "embodies a trilogy of restrictions on expert testimony: qualification, reliability, and fit." *Ruggiero v. Yamaha Motor Corp., U.S.A.*, 778 F. App'x 88, 93 (3d Cir. 2019) (citing *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003)).

1. The Expert Must Be Qualified to Give the Opinion.

As a threshold matter, an expert must be qualified to testify about the subjects on which the expert is offered, which requires "specialized knowledge" regarding the area of the expert's testimony. *See Ruggiero*, 778 F. App'x at 93; *Elcock v. Kmart Corp.*, 233 F.3d 734, 741 (3d Cir. 2000); *Waldorf v. Shuta*, 142 F.3d 601, 625 (3d Cir. 1998). To testify as an expert, a witness must "have such skill, knowledge, or experience in the field as to make it appear that his opinion will probably aid the

trier of fact in his search for the truth." *Aloe Coal Co. v. Clark Equip. Co.,* 816 F.2d 110, 114 (3d Cir. 1987); *see Barrett v. Rhodia, Inc.*, 606 F.3d 975, 982 (8th Cir. 2010) (holding that a psychologist with no training or experience in toxicology was not qualified to offer expert testimony on toxicology). Simply having a "knowledge base superior to a layperson" is insufficient to qualify as an expert. *Higgins v. Koch Dev. Corp.,* 794 F.3d 697, 704 (7th Cir. 2015) (finding treating physician was not qualified to testify as a causation expert merely due to her status as a pulmonologist where she had no training in toxicology or other relevant areas).

A qualified expert may only give an opinion on areas within the expert's area of expertise. *See Calhoun v. Yamaha Motor Corp., U.S.A.*, 350 F.3d 316, 322 (3d Cir. 2003) (allowing experts to testify about proper warnings but excluding additional opinions); *Medalen v. Tiger Drylac U.S.A., Inc.,* 269 F. Supp. 2d 1118, 1129 (D. Minn. 2003) (restricting testimony of toxicologist to the carcinogenicity of the products at issue and not allowing him to opine on anything relating to the etiology of basal cell carcinoma); *United States v. Faines*, 216 Fed. App'x 227, 230 (3d Cir. 2007). An expert may thus be qualified to give an opinion on one subject but not qualified to opine on other areas outside the expert's specialty or area of expertise. *See Pooshs v. Philip Morris USA, Inc.*, 904 F. Supp. 2d 1009, 1019 (N.D. Cal. 2012) (finding epidemiologist qualified to give opinion relating to his expertise

in health behavior, cigarettes, and the addiction properties of nicotine but not qualified to give an opinion relating to cigarette design).

2. The Expert Opinion Must Be Reliable.

Rule 702(c) requires the court find an expert's testimony reliable. To be reliable, scientific expert testimony must be based on "scientific knowledge." *Daubert*, 509 U.S. at 589-90. "The adjective 'scientific' implies a grounding in the methods and procedures of science. Similarly, the word 'knowledge' connotes more than subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 589-90 (internal citations omitted). It must be grounded in scientific principles and methods and thus must amount to more than mere speculation, conjecture, or subjective belief. *See UGI Sunbury LLC v. A Permanent Easement for 1.7575 Acres*, 949 F.3d 825, 834 (3d Cir. 2020) (quoting *Karlo v. Pittsburgh Glass Works, LLC*, 849 F.3d 61, 79 (3d Cir. 2017)).

To determine whether expert testimony is scientifically valid, the district court must focus on the methodologies and data underlying the expert's conclusions to make certain that the conclusions are supported by "good grounds." *Daubert,* 509 U.S. at 590; *In re Paoli R.R. Yard PCB Litig.*, 35 F. 3d 717, 742 (3d Cir. 1994) ("An inquiry into the reliability of scientific evidence under Rule 702 requires a determination as to its scientific validity.") (citing *Daubert*, 509 U.S. at 590 n.9)).

To evaluate the reliability of a particular methodology, the trial court may consider the following factors:

> (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put.

Johnson & Johnson, 509 F. Supp. 3d at 131-32 (citing *United States v. Downing*, 753 F.2d 1224, 1238-39 (3d Cir. 1985)). While the analysis should be focused on the expert's methodology, "it is acceptable for the court to conduct at least a limited review of the expert's conclusions in order to determine whether they could reliably flow from the facts known to the expert and the methodology used." *Id.* (citation and internal quotations omitted)

When analyzing reliability, courts are advised "to determine whether the analysis undergirding the experts' testimony falls within the range of accepted standards governing how scientists conduct their research and reach their conclusions." *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995); *Johnson & Johnson*, 509 F. Supp. 3d at 131 ("[C]ourts must ensure that expert testimony reflects accepted standards within the relevant scientific and business communities."). Courts in the Third Circuit look to the following factors when considering the reliability of a general causation opinion: "whether the expert relied

on epidemiological studies; whether the expert ignored or sufficiently addressed epidemiological studies which contradicted his hypothesis, explaining the discrepancy between his hypothesis and that of the authors; and, whether the findings set forth in the studies are statistically significant." *Pritchard v. Dow Agro Sciences*, 705 F. Supp. 2d 471, 484-85 (W.D. Pa. 2010), *aff'd*, 430 F. App'x 102 (3d Cir. 2011).

"[S]ound scientific methodology requires that a scientist consider all of the scientific evidence when making causation determinations." *Zoloft*, 26 F. Supp. 3d at 463. A failure by an expert to discredit or meaningfully address alternative explanations for studies that find no association or no statistically significant association between the disease and the exposure undermines the reliability of the expert's opinion. *See Zoloft*, 858 F.3d at 799-800 ("Dr. Jewell should have 'sufficiently discredit[ed] other studies that found *no association* or a negative association with much more precise confidence intervals, [or] sufficiently explain[ed] why he did not accord weight to those studies.'"). "Courts may also 'consider whether the authors of the study found the association to be statistically significant and, where the authors found an association to not be statistically significant, an opinion may be unreliable.'" *Johnson & Johnson*, 509 F. Supp. 3d at 164 (citation omitted). Where a disease occurs in the general population, "[t]he need for statistically significant epidemiology is particularly acute" in order "to determine

whether any given case of [the disease] could possibly be attributable to a particular drug." *Soldo*, 244 F. Supp. 2d at 533.

Additionally, when considering the reliability of expert testimony, a court may examine whether there is too great an analytical gap between the data and the opinion proffered. *C.W. ex rel. Wood v. Textron, Inc.*, 807 F.3d 827, 835 (7th Cir. 2015) (citing *Gen. Elec. Co. v. Joiner,* 522 U.S. 136, 146 (1997)) (upholding district court's decision to reject studies relied on by experts where they failed to connect the dots between the studies and the relevant illnesses); *Pritchard*, 705 F. Supp at 485 (citing *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 158 (3d Cir. 1999)). On the whole, a Court must "assure itself that the expert's conclusions are not based upon unreasonable extrapolations from existing data." *Roundup*, 390 F. Supp. 3d at 1134 (citing *Joiner*, 522 U.S. at 146).

An expert's use of unreliable underlying data will also make an opinion unreliable. "If the data underlying the expert's opinion are so unreliable that no reasonable expert could base an opinion on them, the opinion resting on that data must be excluded." *Montgomery Cty. v. Microvote Corp.*, 320 F.3d 440, 448-49 (3d Cir. 2003) (internal citations omitted); *Nationwide Agribusiness Ins. Co. v. Varco Pruden Buildings, Inc.,* 2020 WL 1778069, at *9 (N.D. Tex. Mar. 3, 2020) (excluding expert's conclusions and testimony as inadmissible and unreliable because he relied on the wrong measurements to conduct his analysis); *Burst v. Shell*

Oil Co., 104 F. Supp. 3d 773, 780-81 (E.D. La. 2015) (excluding expert's opinion concerning benzene exposure because expert relied on demonstrably inaccurate estimate regarding amount of benzene vapor in air and error impacted reliability of expert's approach).

3. The Expert Opinion Must Assist the Trier of Fact.

The third prong of admissibility, fit, concerns whether the expert's testimony will help the trier of fact resolve disputed factual issues or understand the evidence. *See Oddi v. Ford Motor Co.*, 234 F.3d 136, 145 (3d Cir. 2000); *Downing*, 753 F.2d at 1235; *Schneider ex rel. Est. of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003); *In re Diet Drugs Prod. Liab. Litig.*, 706 F. 3d 217, n.7 (3d Cir. 2013); *Total Control, Inc. v. Danaher Corp.*, 338 F. Supp. 2d 566, 569 (E.D. Pa. 2004). "The issue of fit 'is one of relevance and expert evidence which does not relate to an issue in the case is not helpful.' . . . The standard for fitness is 'not that high' but is 'higher than bare relevance.'" *In re Hum. Tissue Prod. Liab. Litig.*, 582 F. Supp. 2d 644, 657 (D.N.J. 2008); *see also U.S. v. Ford*, 481 F.3d 215, 220 n.6 (3d Cir. 2007) ("[F]it is a relevance concern.").

The opinion must be consistent with the facts. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert." *Joiner,* 522 U.S. at 146) (excluding expert opinions on animal studies that were too dissimilar

from the facts presented in the case); *see also In re TMI Litig.,* 193 F.3d 613, 670 (3d Cir. 1999), *as amended,* 199 F.3d 158 (3d Cir. 2000) (upholding district court's exclusion of an expert's demonstrative model because it did not accurately simulate the events at issue).

"[I]n a toxic tort case, expert testimony on the issue of general causation meets Rule 702's 'fit' requirement only if the testimony includes an opinion that (1) exposure to the particular substance at issue, (2) in the dose to which the plaintiff was exposed, (3) for the duration in which plaintiff was exposed, (4) can cause the particular condition(s) of which the plaintiff complains." *Amorgianos v. Nat'l R.R. Passenger Corp.*, 137 F. Supp. 2d 147, 163 (E.D.N.Y. 2001), *aff'd,* 303 F.3d 256 (2d Cir. 2002).

II. SCIENTIFIC PRINCIPLES FOR ANALYZING CAUSATION

A. Fundamental Epidemiological Principles

Epidemiology examines whether an agent is capable of causing disease in humans and is therefore central to the general causation inquiry. Reference Manual on Scientific Evidence, at 551-52 (3d Ed. 2011) ("Reference Manual")[9]; *see also Pritchard*, 705 F. Supp. 2d at 483 ("General causation is often established in a toxic tort case through the use of epidemiological studies."). In fact, "[t]he very purpose of epidemiology is to serve the type of testing function required by *Daubert*, *i.e.*, to

[9] *Available at* https://www.fjc.gov/sites/default/files/2015/SciMan3D01.pdf.

discern accurately the effect of a particular agent on a disease against the background of the natural occurrence of the disease in the relevant population." *Soldo*, 244 F. Supp. 2d at 533. "Stated otherwise, epidemiology is the scientific methodology that allows testing of the hypothesis that Substance A causes Effect B." *Id.* Thus, epidemiological studies are the primary method for proving general causation in court. *See* Reference Manual at 551 n.2.

1. The Hierarchy of Epidemiological Studies.

While randomized clinical trials are the gold standard in epidemiology, researchers do not conduct randomized clinical trials on humans where an agent's effects are expected to be harmful. *See* Research Manual at 555. Instead, analytical, observational studies must be used. *See Id.* at 555-56. These studies observe a group of individuals who have been exposed to an agent and compare them with another group of individuals who have not been exposed to the agent. *Id.*

The two main types of observational studies are cohort studies and case-control studies. *Id.* at 556; *see also Roundup*, 390 F. Supp. 3d at 1116. Cohort studies observe defined populations over time in order to compare disease outcomes. Reference Manual at 557. In these studies, researchers attempt to identify factors other than the exposure to an agent that may be responsible for the increased risk of disease. *See id.* at 559. Prospective cohort studies collect information about risk factors in the present and then follow the participants forward in time to see who

develops a disease, while retrospective cohort studies start with participants who have already developed a disease and attempt to reconstruct information about risk factors that occurred in the past for those participants with the disease outcome. *See id.* at 557. Because prospective cohort studies do not require any reconstruction or recollection of past risk factors, they are the textbook standard for supporting the validity of a causal relationship when randomized clinical trials are unavailable.

Case-control studies, on the other hand, involve comparing individuals with the disease (cases) with a group of individuals who do not have the disease (controls) in order to determine the differences in risk factors between the groups. *See id.* at 557. These studies are inherently retrospective and therefore require adequate recollection of past risk factors. *See Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 352 (5th Cir. 2007) (finding "[c]ase-control studies are not per se inadmissible evidence on general causation" but excluding three case-controls studies as unreliable).

2. Relative Risks and Odds Ratios.

Epidemiologists measure the outcomes of observational cohort and case-control studies using metrics known as relative risks ("RR") and odds ratios ("OR"). The results of cohort studies are reported as RR, while the results of case-control studies are reported as OR. *See* Reference Manual at 567-68. However, for general

causation purposes, the concepts are generally interchangeable and both describe the increase or decrease in risk between exposure and disease. *Id.*

Both RR and OR state the strength of an "association" between an exposure to an agent and a disease outcome. *See id.* at 566. Exposure to an agent and a disease are "associated when they occur more frequently together than one would expect by chance." *Id.* at 352. Specifically, RR is the ratio of the probability of an outcome in an exposed group to the probability of the outcome in the non-exposed group. *See id.* at 627. OR is the likelihood that the group with the disease outcome had the exposure of interest compared to the non-diseased group (or control group). *See id.* at 625.

RR or OR of exactly 1.0 means the risk in exposed individuals is the same as unexposed individuals, and there is no association between the agent and the disease—*i.e.*, the disease outcome occurred by chance and not the agent exposure. *See* Reference Manual at 567. RR or OR greater than 1.0 means the risk in exposed individuals is greater than the risk in unexposed individuals. *Id.* RR or OR greater than two may be causal because the outcomes associated with exposure are more likely than not due to the exposure.

Courts generally look for RR or OR of 2.0 or greater to support an inference of causation. *See In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291, 1313-14 (N.D. Fla. 2018); *Pritchard*, 705 F. Supp. 2d at 486 (holding that a

district court should consider the following factors in evaluating an expert's reliance on an epidemiological study: whether RR reached 2.0, the confidence interval, and the range of relative risk values); *Soldo*, 244 F. Supp. 2d at 449-50 (noting RR "significantly below 1.0 means that the exposure is associated with the absence of the disease, whereas [RR] significantly above 1.0 means that exposure is associated with an increased risk of the disease"); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1225-26 (D. Colo. 1998) ("Plaintiffs must present expert testimony demonstrating that exposure to breast implants more than doubled the risk of their alleged injuries.").

3. An Association Must Be Statistically Significant to Support an Inference of Causation.

Because observational studies necessarily employ imperfect sampling, it is possible to observe an association greater than 1.0 due to random error. *See* Reference Manual at 572. Accordingly, statistical conventions must be used to assess whether the result is a true association, *i.e.*, "statistically significant." Specifically, p-values and confidence intervals are used to assess whether a RR or OR is a statistically significant association.

Courts have recognized the principle that an association must be "statistically significant" to support an inference of causation. *Pritchard*, 705 F. Supp. 2d at 486; *Meyers v. Gwin Dredging & Dock, Inc.*, 2005 WL 8175914, at *2 (D.N.J. Dec. 20, 2005) (finding expert opinion failed to rise above unsupported speculation where

statistical significance of studies relied upon was questionable); *Soldo*, 244 F. Supp. 2d at 533 ("The Court concludes that plaintiff's experts' hypothesis about medical causation is not scientifically reliable because it is not based on statistically-significant epidemiologic studies."); *Siharath v. Sandoz Pharm. Corp.*, 131 F. Supp. 2d 1347, 1358 (N.D. Ga. 2001) ("The burden is on Plaintiffs to show that well-conducted epidemiological studies do show a statistically significant relationship between Parlodel(R) and seizures and stroke. It is not Defendant's burden to show the lack of such a relationship."); *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996); *DeLuca v. Merrell Dow Pharm., Inc.*, 791 F. Supp. 1042 (D.N.J. 1992).

a. P-Values

"The p-value is the probability of getting data as extreme as, or more extreme than, the actual data—given that the null hypothesis is true." *See* Reference Manual at 250. "If p is small, the observed data are far from what is expected under the null hypothesis—too far to be readily explained by the operations of chance. That discredits the null hypothesis." *Id.* at 251. P-values of less than 0.05 are typically judged to be statistically significant, indicating that the results of the study are likely to be due to chance less than 5% of the time. *See id.* at 251-52. P-value is related to the study size and is therefore limited in what it conveys. *Id.*

b. Confidence Intervals

A confidence interval provides both the RR or OR and a range (interval) within which the risk likely would fall if the study were repeated numerous times. Reference Manual at 573. A 95% confidence interval, which is the most popular, represents a range in which 95% of time the intervals from repeated samples would cover the true value. *See* Reference Manual at 245-55, 247, 381 ("[I]f 100 samples of the same size were drawn, the confidence interval expected for at least 95 of the samples would be expected to include the true population value"). A confidence interval that includes a value of 1.0 or less, without regard to the upper end of the confidence interval (*e.g.*, 95% CI: 0.8-3.6), indicates that the relationship between the exposure and health outcome is not statistically significant and that the results of the study could be due to chance alone. *See* Reference Manual at 621 ("Where the confidence interval contains a relative risk of 1.0, the results of the study are not statistically significant."); *In re Bextra & Celebrex Mktg. Sales Pracs. & Prod. Liab. Litig.,* 524 F. Supp. 2d 1166, 1174 (N.D. Cal. 2007).

4. Once a Statistically Significant Association Has Been Observed, Scientists Must Apply Bradford Hill Criteria to Determine Whether Causation May Be Inferred.

Because epidemiological studies are designed only to identify statistical relationships between the incidences of disease in one group compared to the incidence of disease in another group, they do not as a matter of course demonstrate

the existence of a causal relationship between an agent and a disease. *See Davis v. McKesson Corp.*, 2019 WL 3532179, at *33 (D. Ariz. Aug. 2, 2019) ("[T]he observed association is the trigger – the starting point – for the causation analysis."). Thus, once a statistically significant association has been observed, epidemiologists use the Bradford Hill criteria to assess whether a true cause-effect relationship may be inferred from the statistical association. *See In re Mirena Ius Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018), *aff'd sub nom. In re Mirena IUS Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 982 F.3d 113 (2d Cir. 2020) ("The Bradford Hill criteria are metrics that epidemiologists use to distinguish a causal connection from a mere association. . . . These criteria start with an association demonstrated by epidemiology and then apply eight or nine criteria to determine whether that association is causal."). The Bradford Hill criteria include:

- **Strength**: How strong is the association between the suspected risk factor and the observed outcome;
- **Consistency**: Does the association hold in different settings and among different groups;
- **Specificity**: How closely are the specific exposure factor and the specific health outcome associated, i.e., how unique is the quality or quantity of the response;
- **Temporality**: Does the hypothesized cause precede the effect;
- **Biological plausibility**: Does the apparent association make sense biologically;
- **Coherence**: Is the association consistent with what is known of the natural history and biology of the disease;

- **Experimental verification**: Does any experimental evidence support the hypothesis of an association;
- **Biological analogy**: Are there examples of similar risk factors and similar outcomes; and
- **Dose-response relationship**: Has a dose-response relationship been established, i.e., does the magnitude of the response increase as the magnitude of the dose increases.

See Reference Manual at 375-79; *see also* Bradford Hill, *The Environment & Disease: Association or Causation*, 58 PROC. ROYAL SOC'Y MED. 295, 295-300 (1965).

Thus, with respect to epidemiology, the scientific method for determining whether a causal relationship exists between exposure to NDMA and/or NDEA and a type of cancer (1) looks for statistically significant associations between NDMA and NDEA and a type of cancer and (2) if found, applies the Bradford-Hill criteria. *See Roundup*, 390 F. Supp. 3d at 1116 ("Once epidemiologists have concluded from the studies that there is an association between an agent and an outcome, they often assess causation through a framework called the 'Bradford Hill criteria.'"); *Zoloft*, 26 F. Supp. 3d at 445 ("To infer a causal relationship from an association, scientists look at well-established factors sometimes referred to as the Bradford–Hill criteria."). If no association is found, chance has not been adequately ruled out and the inquiry ends; consequently, the Bradford Hill criteria should not be applied to determine if there is a causal relationship. *See McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, 2013 WL 3487560, at *15 (W.D. Pa. July 12, 2013) ("If no

association between the exposure and the disease is supported by the scientific literature, there is no basis to find a causal relationship exists and the analysis should end there."); *Soldo*, 244 F. Supp. 2d at 461. If an association is found and an epidemiologist conducts a Bradford Hill analysis, the Court must assess the expert's "'techniques' used to implement the analysis" to ensure they are "1) reliable and 2) reliably applied.'" *Johnson & Johnson*, 509 F. Supp. 3d at 161 (quoting *Zoloft*, 858 F.3d at 796).

B. Fundamental Toxicological Principles

1. Toxicology and the Dose-Response Relationship.

"Toxicology is 'a science that deals with poisons and their effect on living organisms [and] with substances otherwise harmless that prove toxic under particular conditions[.]'" *White v. Esmark Apparel, Inc.*, 44 F.3d 1005 (5th Cir. 1995). Toxicologists determine the adverse effects that a substance will induce in humans and characterize the dose ranges over which exposure to the substance is safe or toxic:

> [T]he relationship between dose and effect (dose-response relationship) is the hallmark of basic toxicology. Dose is the single most important factor to consider in evaluating whether an alleged exposure caused a specific adverse effect. Often low dose exposures—even for many years—will have no consequence at all, since the body is often able to completely detoxify low doses before they do any damage. Furthermore, for most types of dose-response relationships following chronic (repeated) exposure, thresholds exist, such that there is some dose below which even repeated, long-term exposure would not cause an effect in any individual.

McClain, 401 F.3d at 1242. A toxicologist's opinion on causation should include three preliminary assessments: (1) whether the disease can be related to chemical exposure by a biologically plausible theory; (2) whether the plaintiff was exposed to the chemical in a manner that can lead to absorption into the body; and (3) whether the dose to which the plaintiff was exposed is sufficient to cause the disease. Reference Manual at 661.

2. Reliable Toxicology Methods Consider Background Risk, Including Ubiquitous Exposure to NDMA and NDEA.

A reliable methodology should consider the background risk, which is "the risk that everyone faces of suffering the same malady that a plaintiff claims without having exposure to the same toxin." *McClain*, 401 F.3d at 1243. Here, the background risk "is the risk [plaintiffs] and other members of the general public have of suffering [each of] the [cancers] that plaintiff[s] alleges *without* exposure" to the NDMA or NDEA in the VCDs and includes "all those causes of [the cancers], whether known or unknown, excluding the [VCDs]." *Id.*; *see also Chapman v. Procter & Gamble Distrib., LLC*, 766 F.3d 1296, 1307 (11th Cir. 2014) (excluding expert general causation opinions where experts did not know the background risk of the relevant disease); *Abilify*, 299 F. Supp. 3d at 1308 ("[A] failure to identify or describe the background risk of a disease is a "serious methodological deficiency" and "substantial weakness" in an expert's general causation opinion."); *In re Denture Cream Prod. Liab. Litig.*, 795 F. Supp. 2d 1345, 1365 (S.D. Fla. 2011) (noting that

without a baseline of the background risk of a disease, "any incidence could be a coincidence"). If the VCDs do not increase the risk of the adverse effects compared to the risk the general population faces, that would reduce the likelihood that the VCDs harmed plaintiffs. *See McClain*, 401 F.3d at 1243.

3. Reliable Methods Do Not Use the "No Safe Level" Theory.

The "no safe level" or "no threshold" theory "rejects the idea that there might be a threshold at which the neutral or benign effects of a substance become toxic." *Id.* It "cannot be falsified, nor can it be validated. . . . It has no known or potential rate of error. It is merely a hypothesis." *Whiting v. Boston Edison Co.*, 891 F. Supp. 12, 25 (D.Mass. 1995). Accordingly, "it has been rejected by the overwhelming majority of the scientific community[,]" *id.*, as well as federal courts. *See Henricksen v. ConocoPhillips Co.*, 605 F. Supp. 2d 1142, 1165-66 (E.D. Wash. 2009) (citations omitted) ("The use of the no safe level or linear 'no threshold' model for showing unreasonable risk 'flies in the face of the toxicological law of dose-response, that is, that 'the dose makes the poison,' which refers to the general tendency for a greater dose of a toxin to cause greater severity of responses in individuals, as well as greater frequency of response in populations."); *see also Krik v. Exxon Mobil Corp.*, 870 F.3d 669, 677 (7th Cir. 2017) (noting that "more than thirty other federal courts and state courts have held that this cumulative/'any exposure' theory is not reliable").

4. Public Health Guidelines Are Not the Level at Which Harmful Effects Occur.

While causation experts can *consider* public health guidelines, they cannot rely on these guidelines in reaching a causation conclusion because the standards used by government agencies for causation are distinct from those used by the courts:

> The risk-utility analysis [undertaken by agencies like FDA] involves a much lower standard than that which is demanded by a court of law. A regulatory agency such as the FDA may choose to err on the side of caution. Courts, however, are required under the *Daubert* trilogy to engage in objective review of evidence to determine whether it has sufficient scientific basis to be considered reliable.

McClain, 401 F.3d at 1249-50 (internal citation omitted)); *see also Denture Cream*, 795 F. Supp. at 1365 ("[R]egulatory agencies follow different standards than courts in toxic-tort cases."); *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig.*, 174 F. Supp. 3d 911, 923 (D.S.C. 2016); *In re Neurontin Mktg., Sales Pracs., & Prod. Liab. Litig.*, 612 F. Supp. 2d 116, 136 (D. Mass. 2009) ("It is widely recognized that, when evaluating pharmaceutical drugs, the FDA often uses a different standard than a court does to evaluate evidence of causation in a products liability action."); *Allen*, 102 F.3d at 98 (citations omitted) ("Regulatory and advisory bodies such as IARC, OSHA and EPA utilize a 'weight of the evidence' method to assess the carcinogenicity of various substances in human beings and suggest or make prophylactic rules governing human exposure. . . . The agencies' threshold of proof is reasonably lower than that appropriate in tort law, which

'traditionally make[s] more particularized inquiries into cause and effect' and requires a plaintiff to prove 'that it is more likely than not that another individual has caused him or her harm.'").

"Regulatory levels are not meant to represent thresholds for adverse effects" and "courts routinely condemn experts' reliance on regulatory values when attempting to evaluate the risk posed to a particular individual." *Hostetler v. Johnson Controls, Inc.*, 2020 WL 5543081, at *2-3 (N.D. Ind. Sept. 16, 2020). Therefore, expert testimony that directly relies on public health guidelines or that implies the use of risk-benefit analysis does not adequately address the causation question. *McClain,* 401 F.3d at 1250 (finding expert relied on risk-benefit analysis, "which does not directly focus on the question of causation in these four Plaintiffs—the heart of this toxic tort case"); *Lipitor*, 174 F. Supp. 3d at 923 ("With regard to the FDA label, the decision by the FDA to require warnings on a drug label, standing alone, does not suffice to establish causation."); *Denture Cream*, 795 F. Supp. 2d at 1365; *Neurontin*, 612 F. Supp. 2d at 136.

Importantly, and as noted *supra* at [fact section], despite these lower thresholds, no regulatory agency has classified NDMA or NDEA as a known human carcinogen given the dearth of evidence indicating carcinogenicity in humans.[10]

[10]Regulatory agencies have classified NDMA and NDEA as probable or likely human carcinogens based only on evidence from animal studies. *See* Ex. L, Environmental Protection Agency, "Technical Fact Sheet – N-Nitroso-

5. Toxicological, Live Animal Studies Present Disadvantages.

Unlike epidemiologists, toxicologists frequently rely on animal studies, which present significant disadvantages for human causation questions. "[T]he use of animal studies may not be methodologically acceptable to show that chemical X increases the risk of cancer in humans" because, for example, the doses used to induce responses in animals are almost always significantly higher than the exposure humans face. *Paoli*, 35 F.3d at 743; *In re Silicone Gel Breast Implants Prod. Liab. Litig.*, 318 F. Supp. 2d 879, 891 (C.D. Cal. 2004) ("[T]oxicological expert opinions are 'almost always' based on animal studies that involve doses of a suspected carcinogen that are significantly higher than animal doses comparable to expected human exposure."); Reference Manual at 646 ("[T]he dose at which mercury causes this effect in laboratory animals is modified by many internal factors, and the exact dose–response curve may be different from that for humans.").

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dimethylamine (NDMA)," at 3 (January 2014), *available at* https://www.epa.gov/sites/default/files/2014-03/documents/ffrrofactsheet_contaminant_ndma_january2014_final.pdf (last accessed Oct. 11, 2021) (classification of NDMA by Environmental Protection Agency ("EPA") as Group 2B, meaning probable human carcinogen" "based on the induction of tumors in both rodents and nonrodent mammals"); Ex. M, National Toxicology Program, *Report on Carcinogens* (14th Ed., 2016) at 5, 7, *available at* https://ntp.niehs.nih.gov/ntp/roc/content/profiles/nitrosamines.pdf (last accessed Oct. 11, 2021) (classification of NDMA and NDEA by National Toxicology Program as "reasonably anticipated" to be "human carcinogens" based on "sufficient evidence of carcinogenicity from studies in experimental animals").

A bioassay is a "test for measuring the toxicity of an agent by exposing laboratory animals to the agent and observing the effects." *See* Reference Manual at 680. Lifetime bioassays were developed because exposures may continue throughout a lifetime, and these tests use relatively high doses given to the experimental animals. *See id.* at 648. Indeed, the standard protocol for performing chronic animal cancer bioassays includes testing the chemical at its maximum tolerated dose (MTD). *See id.* at 644. Theoretically, the MTD is the highest dose at which the normal bodily functions of the animal are not *significantly* interrupted, and the intended purpose of the MTD is to ensure that the carcinogenic potential is not missed on the basis of the dose selected. *See id.* at 682.

Because the animal test doses are so high, and humans are frequently exposed to levels of the chemical that are orders of magnitude lower, these high-dose animal findings may easily have no, or at best, limited relevance to the lower exposure levels experienced by human populations. *See id.* at 645-45. "The interpretation of results requires extrapolation from animals to humans, from high to low doses, and from short exposures to multiyear estimates." *Id.*

Therefore, for animal studies to be admissible as causation evidence, an expert must have "good grounds to extrapolate from animals to humans, and the methodology of the studies must constitute good grounds to reach conclusions about the animals themselves." *Paoli*, 35 F.3d at 743. Courts exclude animal studies where

the expert did not analyze and review the similarities and differences between humans and the animal species in which the agent was tested. *See Silicone Gel Breast Implants*, 318 F. Supp. 2d at 891 (collecting cases);[11] *see also* Reference Manual at 661 ("The expert should review similarities and differences between the animal species in which the compound has been tested and humans.").

ARGUMENT

Plaintiffs cannot meet Rule 702's rigorous standards. As a preliminary matter, Dr. Hecht's opinion is focused on liability and does not address the general causation question at issue at this stage of the litigation. Prior to his deposition, the parties agreed that the majority of Section III of Dr. Hecht's report, which contains the lion's share of the novel opinions and analysis in the report, is inapplicable to the general causation question. Section I of Dr. Hecht's report contains information on his background and qualifications, and section II is merely a recitation of basic information on nitrosamines. While we address Dr. Hecht's boilerplate general causation statement in detail below, as a threshold matter Dr. Hecht's report and opinions simply are not a fit for general causation, and the Court should exclude him entirely at this stage of the litigation.

[11] Additionally, "[a]nimal studies are not generally admissible where contrary epidemiological evidence in humans exists." *See Silicone Gel Breast Implants*, 318 F. Supp. 2d at 891 (citing *Richardson v. Richardson–Merrell, Inc.*, 857 F.2d 823, 830 (D.C.Cir. 1988), *cert. denied,* 493 U.S. 882 (1989)).

To the extent his report even attempts to address general causation, it is not the result of a reliable methodology, and his belief that NDMA and NDEA are "risk factors" for cancer does not fit the case. Accordingly, as shown below in greater detail, this Court should exclude Dr. Hecht's opinions in their entirety at this stage.

A. Methodology

Dr. Hecht's general causation opinions in this case are unreliable and should be excluded. *See Whyte v. Stanley Black & Decker, Inc.*, 514 F. Supp. 3d 684, 694 (W.D. Pa. 2021) (finding plaintiff's proffered expert qualified, but nonetheless excluding the expert's testimony because it was not sufficiently reliable).

1. Dr. Hecht Failed To Consider Any Dose Threshold For His Conclusion That NDMA And NDEA Are Capable Of Causing Cancer In Humans At The Levels Present In Defendants' VCDs.

"***Dose matters***." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig. (No II) MDL 2502*, 892 F.3d 624, 639 (4th Cir. 2018) (modification omitted; emphasis supplied). "A central tenet of toxicology is that the 'dose makes the poison' and that all chemical agents, including water, are harmful if consumed in large quantities." *Mancuso v. Consol. Edison Co. of New York*, 967 F. Supp. 1437, 1445 (S.D.N.Y. 1997) (citation omitted). Dr. Hecht agrees.

Q: Do you also understand and can we agree that the question of whether a substance is capable of causing cancer is dependent on dose and duration of exposure?
A: Yes.

***

Q: And are you familiar with the old adage that "The dose makes the poison?"
A: Yes.
Q: Do you agree with that statement?
A: Yes.

***

Q: Water is a life-sustaining substance, correct?
A: Yes.
Q: However, water can be deadly when it's consumed to excess; true?
A: Yes.

(Ex. N, Hecht Dep. Tr. 26:23-27:2, 27:15-19, 28:3-5.)

Given Dr. Hecht's recognition that dose and duration are significant in a general causation analysis, it is remarkable that Dr. Hecht never conducted any research to evaluate or establish a threshold dose—a dose below which there would be no detrimental effect—for either NDMA or NDEA in humans. (*Id.* 81:11-82:3, 167:6-22, 209:4-7.) Ignoring the dose-response relationship, Dr. Hecht simply opines that there is no safe threshold for NDMA and NDEA in the VCDs.

Q: Do you have any evidence to suggest to this jury that a plaintiff in this litigation who consumed valsartan-containing medication that came from Mylan ever received a pill that contained nitrosamines above the PDE established by Johnson and his colleagues?
A: No, I don't.[12]

[12] In fact, Hecht did not perform any calculations using any manufacturers' data to establish that any pill Plaintiffs may have consumed contained NDMA or NDEA above the PDE established by Johnson and his colleagues. Regardless of the manufacturer (Aurobindo, Mylan, ZHP, Teva, Hetero, or Torrent), he conceded that

> Q: Earlier in the deposition - -
> A: No, it's still maintained that none of that should be there. It should be zero.

(*Id*. 211:6-15; *see also id.* 369:9-23 [stating that "I believe there is no threshold"].)

Dr. Hecht conducted no research to support his theory, which is inconsistent with basic toxicological principles.

> The use of the no safe level or linear "no threshold" model for showing an unreasonable risk flies in the face of the toxicological law of dose-response, that is, that the dose makes the poison, which refers to the general tendency for a greater dose of a toxin to cause greater severity of responses in individuals, as well as greater frequency of response in populations.

Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1165-66 (E.D. Wash. 2009) (internal quotation omitted) (citation omitted). Courts have rejected such theories for decades. *See, e.g., Whiting v. Boston Edison Co.*, 891 F. Supp. 12, 25 (D. Mass. 1995) ("The linear non-threshold model cannot be falsified, nor can it be validated. To the extent that it has been subjected to peer review and publication, it has been rejected by the overwhelming majority of the scientific community. It has no known or potential rate of error. It is merely an hypothesis.") In fact, "reach[ing] conclusions about human toxicity without careful consideration of dose-response is

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FDA determined reasonably safe levels for human consumption and he has not done any alternative risk assessment to suggest otherwise. (*Id.* 167:6-22, Aug. 17, 2021 [stating "I haven't made any calculations. That's up to FDA, EMA, and the risk assessors. That's not what I do."].)

a 'significant methodological flaw' under *Daubert*." *In re Zoloft (Sertraline Hydrocloride) Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 478 (E.D. Pa. 2014).

Dr. Hecht's willingness to ignore the dose-response relationship illustrates the outcome-driven nature of his opinion. Dr. Hecht reaches his conclusions without proper consideration of the dose-response relationship and the levels of NDMA and NDEA that Plaintiffs may have been exposed to from Defendants' VCDs. This fatal methodological flaw renders his opinions unreliable, and thus, inadmissible. *See In re Lipitor (Atorvastatin Calcium) Mktg. Sales Practices & Prods. Liab. Litig.*, 2015 WL 6941132, at *1 (D.S.C. Oct. 22, 2015) (stating that "Plaintiffs must demonstrate, at general causation, that particular doses of [the drug] are capable of causing [the disease]"); *In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d 887, 895 (E.D. Ark. 2010) (stating that "if an expert's opinion does not specify what level of exposure increases the risk of adverse health effects, the opinion may be deemed unreliable" and precluding expert testimony where expert failed to specify dose or exposure levels of estrogen necessary to cause breast cancer, but merely asserted that "estrogen is carcinogenic") (citation omitted).

2. Dr. Hecht's Opinions Are Unreliable Because He Extrapolates From Dissimilar Animal Studies.

To support his opinion that NDMA and NDEA at the trace levels found in Defendants' valsartan can cause cancer in humans, Dr. Hecht relies on a host of

animal studies that, by his own admission, bear no semblance to the levels of exposure potentially at issue in litigation. The Third Circuit has recognized:

> [A]nimal studies may be methodologically acceptable to show that chemical X increases the risk of cancer in animals, but they may not be methodologically acceptable to show that chemical X increases the risk of cancer in humans. . . . [I]n order for animal studies to be admissible to prove causation in humans, there must be good grounds to extrapolate from animals to humans, just as the methodology of the studies must constitute good grounds to reach conclusions about the animals themselves.

In re Paoli, 35 F.3d at 743; *see also Hall v. Baxter Healthcare Corp.*, 947 F. Supp. 1387, 1410 (D. Or. 1996) ("Extrapolations of animal studies to human beings are generally not considered reliable in the absence of a scientific explanation of why such extrapolation is warranted.").

Here, as recognized by the authors of the animal studies on which Dr. Hecht relies, extrapolation is not warranted. For example, the Peto study,[13] relied upon by Dr. Hecht for his "no threshold" theory, states that "[i]t would be a serious distortion of these experimental results to extrapolate this data to humans."

> Q: In his work, Peto was careful to note that no extrapolation of this data to humans should be done.
> Do you agree?
> A: Yes.
>
> ***

[13]Ex. U, Peto, R., et al. "Effects on 4080 Rats of Chronic Ingestion of N-Nitrosodiethylamine or N-Nitrosodimethylamine: A Detailed Dose-Response Study."

Q: When we talk about humans, Peto's study does not provide us with any reliable information. He even said so, right?
A: That's what he says. It says it right there.

(Hecht Dep. Tr. 123:10-14, 125:9-15.) In another study relied upon by Dr. Hecht, the authors again cautioned against extrapolating the animal study data to humans.

Q: Gombar says once again that extrapolation of carcinogenicity data from laboratory animals to humans is a difficult task because chemical carcinogenesis is a multistep process involving many factors, right?
A: True.

***

Q: Do you agree with all that sir?
A: Yes, I do.

(*Id*. 126:12-21.) At bottom, Dr. Hecht had to agree that the authors of the animal studies he relied on in his report consistently warn against using the data to extrapolate carcinogenicity in humans. (*Id*. 127:4-9.) Dr. Hecht further agrees that it is difficult to extrapolate animal studies to humans and there is species to species variation. (*Id*. 70:10-12, 74:9-15.)

Separate and apart from extrapolation to humans being unwarranted in this case, Dr. Hecht's reliance on these animal studies is misplaced because the doses administered to the test animals were orders of magnitude higher than Plaintiffs' potential exposures. With regard to one of Dr. Hecht's own studies that compared

NNK (a TSN) to NDMA,[14] Dr. Hecht stated that the test rats were exposed to doses orders of magnitude higher, or "significantly higher," than the nitrosamine levels present in Defendants' VCDs. (*Id.* 72:10-14, 72:20-25; *see also id.* 119:18-23 [agreeing that the doses administered to rats in the Magee and Barnes study[15] were orders of magnitude greater than what Plaintiffs would have been exposed to by VCDs]; 128:22-130:20 [same with respect to the doses in one of the Gombar studies[16]].) Dr. Hecht's reliance on animal studies that—by his own admission—dosed animals with nitrosamines at levels orders of magnitude greater than any nitrosamine present in Defendants' VCDs renders his opinion unreliable. *See Soldo*, 244 F. Supp. 2d at 530, 547 (finding the plaintiff's experts' methodology "scientifically invalid and unreliable" where it relied on animal studies admittedly "hundreds and thousands of times higher" than what humans were experiencing and concluding that the plaintiff's "experts fail[ed] to take into account critical differences between animal data and human experience—including but not limited to extrapolations in dosing").

[14]Ex. O, Hecht, S., et al. "Comparative Tumorigenicity and DNA Methylation in F344 Rats by 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone and N-nitrosodimethylamine"

[15]Ex. P, Magee, P.N., & Barnes, J.M., "The Production of Malignant Primary Hepatic Tumours in the Rat by Feeding Dimethylnitrosamine"

[16] Ex. Q, Gombar, C.T., et al., "Pharmacokinetics of N-nitrosodimethylamine in Swine"

Furthermore, the animal studies upon which Dr. Hecht relies contradict the only epidemiological studies analyzing the effect—or lack thereof—of NDMA and NDEA exposure from valsartan in humans—Pottegard[17] and Gomm[18]. The Pottegard cohort study was a 2020 Danish study wherein the authors followed roughly 5,150 Danish patients who had used valsartan. The study followed the individuals for a median of 4.6 years and examined cancer rates in valsartan users as compared to a cohort of non-valsartan users. Dr. Hecht admitted, as he must, that the Pottegard study concluded that there was no evidence of a markedly increased short-term overall risk of cancer from the valsartan containing NDMA. (Hecht. Dep. Tr. 275:7-11.) Similarly, the Gomm study used a German registry database to look at over 750,000 individuals who had filled valsartan prescriptions and compared the incidence of cancer to non-valsartan users. Just like the Pottegard study, the Gomm study found no evidence of an overall increase in cancer risk. (*Id*. 283:14-19.) These two studies further undermine Dr. Hecht's opinion and reliance on animal studies and demonstrate that his opinion is not reliable. *See In re Zoloft*, 176 F. Supp. 3d at 494 (E.D. Pa. 2016) (finding that expert "opinions d[id] not support general

[17] Ex. R, Pottegard, A., et al., "Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study"
[18] Ex. S, Gomm, W., et al., "N-Nitrosodimethylamine-Contaminated Valsartan and the Risk of Cancer"

causation" and noting that "animal studies cannot overcome the contrary results of human epidemiological studies").

3. Dr. Hecht's Opinion Is Unreliable Because, By His Own Admission, He Employed No Recognizable Methodology.

Expert testimony is "reliable" when it is based upon sound methodology and technique. *Paoli*, 35 F.3d at 742. The touchstone is whether the expert's methodology is "sufficiently reliable so that it will aid the jury in reaching accurate results." *Id*. at 744 (internal quotations omitted). An expert opinion cannot be based on "subjective belief and unsupported speculation." *UGI Sunbury LLC v. A Permanent Easement for 1.7575 Acres*, 949 F.3d 825, 834 (3d Cir. 2020).

> A court considers various factors to determine whether the testimony is supported by "good grounds," including: (1) whether a method consists of a testable hypothesis; (2) whether the method has been subject to peer review; (3) the known or potential rate of error; (4) the existence and maintenance of standards controlling the technique's operation; (5) whether the method is generally accepted; (6) the relationship of the technique to methods which have been established to be reliable; (7) the qualifications of the expert witness testifying based on the methodology; and (8) the non-judicial uses to which the method has been put. ¶ Implicit in these factors is that the expert's testimony is based on a discernable methodology, which the Court may assess by applying these factors to it. But if there is no discernable methodology, the Court need not—indeed cannot—apply the "good grounds" factors.

Whyte, 514 F. Supp. 3d at 694 (internal citations and parentheticals excluded).

Dr. Hecht has done no independent testing or analysis related to nitrosamine exposure from Defendants' VCDs. (Hecht Dep. Tr. 163:19-22, 312:25-10, 318:12-19.) Furthermore, Dr. Hecht agrees that a mere association between NDMA and

NDEA and cancer is not enough to establish causation without more research. (*Id.* 247:2-13.) This concession, however, does not stop him from opining that causation is established here based on nothing more than his own subjective belief. Dr. Hecht failed to engage in any Bradford Hill analysis and, in making the leap from association to causation, he admitted that he followed no formal or recognized evaluation or methodology.

> Q: Did you employ the Bradford Hill criteria in this case or utilize the Bradford Hill criteria to determine whether the strength of association in some of these studies merited making the leap to causation?
> A: No, I did not.
> ***
> Q: So you drew conclusions from the literature based on you – given that you're familiar with it and experienced in the subject?
> A: Yes.
> Q: But you did not follow any recognized methodology for making the leap from association to causation?
> A: It was not a formal - -
> ***
> A: It was not a formal evaluation.

(*Id.* 249:25-250:5, 251:21-252:3, 253:23.)

It is no wonder Dr. Hecht had to span this gulf with his own *ipse dixit* considering that there is no scientific evidence establishing NDMA and NDEA as known causes of human cancer. (*Id.* 132:13-18.) Dr. Hecht knows of no peer reviewed literature identifying either NDMA or NDEA as a known cause of human cancer. (*Id.* 132:19-25, 133:1-5.) Dr. Hecht is not aware of any epidemiological study that has found NDMA or NDEA to be a known cause of cancer in humans.

(*Id*. 133:23-134:3.) According to Dr. Hecht, there is no article or study anywhere concluding that a patient's cancer was caused by NDMA or NDEA. (*Id*. 134:4-21.) Nor could he identify any article or study that concludes exogenous NDMA or NDEA intake in food causes cancer. (*Id*. 245:12-246:8, 246:16-247:1.) And finally, he did not cite any studies suggesting that exogenous intake of NDMA or NDEA were the cause of the various cancers alleged by Plaintiffs. (*Id*. 252:24-256:19.)

Dr. Hecht acknowledges that formulating a meaningful and reliable opinion on a causality of exposure to a disease requires an evaluation of the totality of the evidence. (*Id*. 99:7-12.) In this regard, Dr. Hecht did not do anything of the sort. He simply cherry-picked literature that supports his subjective belief that all nitrosamines cause cancer, while disregarding adverse conclusions from the most relevant studies—Pottegard and Gomm.

Q: In any event, what Pottegard reported was that there was no evidence of a markedly increased short term overall risk of cancer from the valsartan containing NDMA, correct?
A: Yes.
Q: You cite to Pottegard in your report that you prepared for this case, right?
A: Yes.

***

Q: When you put this report together, you already told me that one of the questions that was at the heart of this was whether or not NDMA can cause cancer in humans, correct?
A: Yes.
Q: So when you cite to - - here, we have a study like Pottegard that aims to answer that very question, right?
A: Yes.

Q: When you cite to Pottegard in your report, you make no mention at all of the authors' conclusion that NDMA in valsartan was not found to increase the short term overall risk of cancer?
A: No.
Q: Right? Never mention that?

***

A: All right. That's an oversight. I should have mentioned it.

(*Id*. 275:7-14, 276:24-277:13, 277:22-23.)

In fact, there are two—and only two—studies that have examined the risk of cancer from ingestion of VCDs, and Dr. Hecht conveniently ignored ***both of them***.

Q: Gomm was a study where they used the German registry database to look at over 750,000 individuals who filled valsartan scripts, right?
A: Yes.

***

Q: Did you find the conclusions in this study to be reliable?

A: Yes, but it needs confirmation.

***

Q: In terms of overall risk of cancer, Gomm found no evidence of such an increased risk; true?
A: Correct.
Q: The conclusion is Pottegard, correct?

A: Yes.

***

Q: My question is did you ever mention that in your report?

A: We already did that. I already told you that was an oversight . . .

***

A: You know, none of us are perfect. Sometimes we make mistakes.

(*Id*. 282:13-17, 283:4-6, 283:14-19, 286:7-12, 286:16-17.)

As recently explained by the United States District Court for the Southern District of New York,

> [a]n expert must not cherry-pick from the "scientific landscape and present the Court with what he believes the final picture looks like." *In re Rezulin Prod. Liab. Litig.*, 309 F. Supp. 2d 531, 563 (S.D.N.Y. 2004) ("Rezulin") (citation omitted). Sound scientific methodology in assessing general causation requires an expert to evaluate "all of the scientific evidence when making causation determinations." *In re Zoloft (Sertraline Hydrocloride) Prod. Liab. Litig.*, 26 F. Supp. 3d 449, 463 (E.D. Pa. 2014); *see also In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291, 1311 (N.D. Fla. 2018) ("[The] 'weight of the evidence' approach to analyzing causation can be considered reliable, provided the expert considers all available evidence carefully and explains how the relative weight of the various pieces of evidence led to his conclusion."). Cherry-picking is a form of "[r]esult-driven analysis," which "undermines principles of the scientific method" by "applying methodologies (valid or otherwise) in an unreliable fashion." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Practices & Prod. Liab. Litig. (No II) MDL 2502*, 892 F.3d 624, 634 (4th Cir. 2018). Therefore, exclusion of proffered testimony is warranted where the expert fails to address evidence that is highly relevant to his or her conclusion. *See Mirena II*, 341 F. Supp. 3d at 242.

Daniels-Feasel v. Forest Pharms., Inc., 2021 WL 4037820, at *5 (S.D.N.Y. Sept. 3, 2021).

Simply put, Dr. Hecht's opinion is not the result of any recognized or formal methodology. Dr. Hecht's report and testimony is nothing more than his subjective belief, unsupported by any peer-reviewed literature or study. In such circumstances, expert testimony must be excluded. *See Fedor v. Freightliner, Inc.*, 193 F. Supp. 2d 820, 829–30 (E.D. Pa. 2002) ("While his speculation is informed by his training and

experience . . ., [the expert's] opinions . . . clearly lack any identifiable methodology which defendants could challenge.").

4. Dr. Hecht's Opinion Is Unreliable Because He Did Not Establish That NDMA And NDEA In The VCDs Significantly Increased NDMA Or NDEA Exposure Over Background Exposure.

"A reliable methodology [] should take into account the background risk for the disease at issue in the case." *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018) (citing *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1243 (11th Cir. 2005)). Dr. Hecht is of the opinion that nitrosamine intake increases the risk of cancer, but he fails to consider the endogenous and exogenous nitrosamine exposures to which individuals are exposed on a daily basis.

First, Dr. Hecht wholly ignores the endogenous formation of nitrosamines, despite conceding its occurrence. (*See* Hecht Dep. Tr. 94:12-15.) Dr. Hecht acknowledges that peer-reviewed literature suggests that endogenous formation of NDMA and NDEA occurs at high levels exceeding exogenous intake. (*Id.* 190:13-22.) Indeed, this fact is established in the very literature cited in Dr. Hecht's report. (*See id.*; Hecht Rep. 7 n.12 [citing Gushgari].) Yet, Dr. Hecht, like Plaintiffs' other experts, has not done any independent research to quantify the levels of NDMA and NDEA that are formed endogenously. (Hecht Dep. Tr. 194:20-195:2.) Dr. Hecht simply states that he does not know that endogenous formation occurs, but he cannot rule out that it does occur. (*Id.* 202:21-203:1.)

Moreover, Dr. Hecht agrees with the Gushgari[19] study finding that humans are exposed to 2,000 to 25,000 nanograms ***per day*** (ng/day) of nitrosamines, depending on a given individual's habits. With regard to smokeless tobacco users, Gushgari estimated a daily exposure of 21,800 ng/day plus or minus 4,350 ng/day. (*Id*. 176:1-4, 178:20-23.) Even with regard to non-drinkers and non-tobacco users, daily nitrosamine exposure is estimated at 2,000 ng/day from food alone. (*Id.* 178:24-179:18.) Enjoying a cold glass of beer after a long day of work would add another 1,000 ng/day. (*Id*. 176:17-22.)

Dr. Hecht concedes, as he must, that exposures to NDMA and NDEA through VCDs are significantly less than even the lowest estimated daily exposure. Using the mean NDEA found in Mylan's valsartan by way of example (150 ng/day), a tobacco user taking Mylan's valsartan would increase his or her daily intake of nitrosamines by a meager 0.6%. (*Id*. 182:8-19.) Even a clean-living individual (a non-smoker teetotaler) would only increase his daily nitrosamine intake by 7.5%. (*Id*. 182:20-183:5.) ***And, by Dr. Hecht's admission, there exists no peer-reviewed scientific literature that has ever been published suggesting that a modest one to seven percent increase in nitrosamine concentrations over a limited period would cause cancer in humans.*** (*Id*. 183:6-23.)

[19]Ex. T, Gushgari, A., et al., "Critical review of major sources of human exposure to *N*-nitrosamines"

Dr. Hecht's report fails to account for these background exposures and background risks that humans experience every single day—levels, which, according to-peer reviewed literature, are significantly higher than those present in Defendants' VCDs. Dr. Hecht's failure to take these exposures into account is a serious methodological deficiency and his inability to identify any scientific literature stating that a miniscule increase in daily nitrosamine exposure will cause cancer in humans demonstrates that his opinion is not reliable and not based on "good grounds."

B. Dr. Hecht's Testimony Does Not Assist the Trier of Fact and, Therefore, Does Not "Fit" the Case.

Even if the Court were to find his opinion to be the result of a reliable methodology, the Court should still exclude Dr. Hecht's testimony since it is not helpful to the trier of fact. *See Pritchard*, 705 F. Supp. 2d at 492 ("However, even if the Court had found [plaintiffs' expert's] methodology to be reliable, his proffered opinions would be excluded as they do not 'fit' this case.").

Dr. Hecht's testimony makes clear that his opinion is not a true general causation opinion, so it cannot assist the trier of fact in determining whether the levels of NDMA and NDEA present in Defendants' VCDs are capable of causing cancer in humans. Dr. Hecht testified that each Plaintiff is different, that people react differently to nitrosamines, and that you must look at each person individually to

determine the effect of NDMA and NDEA exposure. (Hecht Dep. Tr. 504:2-17.) Such testimony is the antithesis of general causation.

The question Dr. Hecht needed to answer as to general causation was whether NDMA and NDEA, at the trace levels present in Defendants' VCDs over a period of no more than six years, can cause cancer in humans. *See In re Roundup*, 390 F. Supp. 3d at 1108 (stating that the question of general causation is whether a product or substance can cause a disease "at exposure levels people realistically may have experienced"). Dr. Hecht failed to answer that question and his opinion will not be helpful to the jury. *See In re Prempro Prods. Liab. Litig.*, 738 F. Supp. 2d at 895 (finding opinion not probative of whether estrogen increases the risk of breast cancer where expert "has not explained how allegedly harmful effects of [estrogen] can be extrapolated reliably from laboratory studies" and the expert did not "identif[y] a particular dosage of estrogen that results in an increased risk of breast cancer").

Beyond that glaring contradiction, Dr. Hecht's ultimate opinion that he intends to offer is that increased nitrosamine intake is a risk factor for cancer. (Hecht Dep. Tr. 26:9-13; *see also id.* 30:10-13 ["my conclusion was that it posed . . . an unacceptable risk to people taking these medications"].) Obviously, Dr. Hecht agrees that there are multiple risk factors for cancer, including old age, family history, tobacco use, alcohol use, and obesity, to name just a few. (*Id.* 24:6-13, 25:23-26:8.) And Dr. Hecht also agrees that just because something is a risk factor for

cancer, that does not mean that it caused or will cause cancer. (*Id*. 26:14-18.) Thus, at most, Dr. Hecht is offering an opinion on association—it does not rise to the level of general causation. *See, e.g., Magistrini v. One Hour Martinizing Dry Cleaning,* 180 F. Supp. 2d 584, 591 (D.N.J. 2002) (quoting Michael D. Green, et al., Reference Manual on Scientific Evidence at 336-37 (2d ed. 2000)) (noting that "an association is not equivalent to causation"); *see also Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996) (where no epidemiologic study has found a statistically-significant link between the product and the alleged injury, expert testimony of an association does not meet the standard of reliability required under *Daubert*).

CONCLUSION

Based on the above-cited authority, Defendants respectfully request that the Court exclude Dr. Hecht's opinions.

Dated: November 1, 2021

Respectfully Submitted:

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on November 1, 2021, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ Seth A. Goldberg
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